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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/413,785	10/07/99	MANOLAGAS S	D6156

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EXAMINER	
MAYO,K	
ART UNIT	**PAPER NUMBER**
1633	2

DATE MAILED: 12/23/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/413,785	Manolagas et al.
Examiner	**Group Art Unit**
Kris Pelham Mayo	1633

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-14 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-14 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Priority

Applicant's claim for priority to U.S. Provisional Application number 60/116,409, filed on 01/19/1999, and U.S. Provisional Application number 60/103,385, filed on 10/07/1998 is acknowledged. Priority has been perfected.

Drawings

This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed. Note the enclosed PTO Form 948 Notice of Draftsperson's Patent Drawing Review outlining the objections to the drawings in the instant application.

Specification

The disclosure is objected to because of the following informalities:

Several minor typographical errors exist such as those found on page 19, line 1, where "inhallation" is misspelled.

Appropriate correction of this typographical error and any others is necessary.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening for a compound that stimulates bone formation by decreasing osteoblast apoptosis in a mouse animal model, comprising the steps of 1)administering to a mouse animal model selected from the group consisting of a SAMP6 mouse, and a SAMR1, a putative anti-apoptotic compound; 2)determining the number of said cells undergoing apoptosis; and 3)comparing the number of apoptotic osteoblast cells in the mouse model with the number of apoptotic osteoblast cells in a control animal, wherein fewer apoptotic osteoblast cells in the mouse model following administration of said compound indicates that said compound inhibits apoptosis, thereby resulting in stimulation of bone formation; and the above method further comprising the step of first treating the mouse animal model with a systemic glucocorticoid compound, AND while the specification is enabling for an *in vitro* method of screening for a compound that stimulates bone formation by decreasing osteoblast apoptosis, comprising the steps of 1)contacting osteoblast cells with a putative anti-apoptotic compound in a test culture; 2)determining the number of said cells undergoing apoptosis; and 3) comparing the number of apoptotic osteoblast cells with the number of apoptotic osteoblast cells in a control culture, wherein fewer apoptotic osteoblast cells in the test culture indicates that said compound inhibits

apoptosis thereby resulting in stimulation of bone formation; and the above method further comprising the step of first contacting the osteoblast cells with a glucocorticoid compound, does not reasonably provide enablement for a method of contacting osteoblast cells with a test compound in an *in vivo* murine animal model. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. While the specification teaches the method of an *in vitro* assay, and the separate method of screening using systemic administration of a test compound in an animal model, the specification does not teach one of skill in the art how to go about contacting osteoblast cells with both a glucocorticoid compound and a test compound in an intact mouse. Even if local injection was made adjacent to the bone, would the compound of interest "contact" the osteoblasts of interest? Physical and physiological interactions of the subcutaneous, muscle, connective, and periosteal tissues, for example could have an unpredictable effect on the compound of interest such that it does not reach the tissue of interest in active form. Additionally, the specification does not teach what effect the local administration of either glucocorticoids or PTH would have on osteoblasts and apoptosis of osteoblasts. At the time the invention was made, direct application of parathyroid hormone (PTH) to bone was known to be unpredictable. Cornish et al (1995) teach that in mice that received local injections of PTH at the right hemicalveria, an overwhelming increase in bone resorption and an inhibition of bone formation in the bone immediately adjacent to the injection site was seen. However, the uninjected left hemi-calveria showed an increase in bone formation, possibly due to a systemic

anabolic effect of PTH on bone. It would have necessitated undue experimentation on the part of the practitioner to determine an effective method of administration to be able to contact osteoblast cells of an intact mouse with a putative anti-apoptotic compound. Therefore, claims 6-14 are extremely broad. The courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application. See 27 USPQ2d 1662 *Ex parte Maizel*. Scope of Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). In view of the quantity of experimentation necessary to determine the parameters listed above, the lack of direction or guidance provided by the specification, the absence of working examples for the demonstration or correlation to the ability to contact osteoblast cells in an intact mouse with a test compound, the unpredictable state of the art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and/or use the invention as broadly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 7, 10, and 11-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-5 are indefinite in their recitation of human parathyroid hormone [hPTH(1-34)]. It is not clear from this format whether there are many isoforms of human parathyroid hormone and the claims only read on hPTH(1-34), or there is only one human parathyroid hormone, and that is human parathyroid hormone (1-34), abbreviated as hPTH(1-34). The specification appears to disclose specifically human parathyroid hormone (1-34). Therefore, it is recommended that "human parathyroid hormone (1-34), [hPTH(1-34)]" be incorporated into the claim language.

Claims 1-5 are indefinite in their recitation of "individual", as in claim 1. It is not clear if this individual is an animal, tissue, organ or cell, for example. In the absence of clarity, the metes and bounds of the claimed invention cannot be determined. It is recommended that the specific individual being treated be incorporated into the claim language.

Claims 1-5 recite the limitation "such treatment" in claim 1. There is insufficient antecedent basis for this limitation in the claim. Because no reference is made to any treatment previously in the claim, it is not clear what treatment this is referring to. It is recommended that the specific disease, disorder, or pathological process being treated be incorporated into the claim language.

Claim 3 is indefinite in its recitation of "previously". It is not clear what time period this encompasses. Will there be a difference if the patient was treated with glucocorticoid compounds 10 years prior to the administration of hPTH(1-34), as opposed to a patient treated with glucocorticoid compounds 1 day prior to the administration of hPTH(1-34)? Additionally, at the time the invention was made, it was known in the art that PTH treatment would be less effective if

bone loss, such as from prolonged glucocorticoid treatment, had progressed to the stage where trabecular number was already severely depleted. See Meng et al. (1996), page 428, column 1. In the absence of guidance in the specification, the metes and bounds of the claimed invention cannot be determined. It is recommended that the specific period of time be incorporated into the claim language. Applicant is reminded that such an amendment cannot include the addition of any new matter.

Claims 7, 12, and 13 are indefinite in their recitation of "said contacting...is selected from the group consisting of *in vitro* osteoblast cells and an *in vivo* murine animal model." in claims 7 and 12. The phrase is vague and indefinite, because *in vitro* osteoblast cells and an *in vivo* murine animal model are not species of "contacting". In the absence of clarity, the metes and bounds of the claimed invention cannot be determined. Furthermore, it is unclear how contacting of osteoblast cells can occur with systemic (subcutaneous) administration of PTH. It is also unclear if the term "contacting" means direct contact only, such as direct application of the PTH to isolated cells in a culture, or indirect contact, such as where an active form of the administered PTH reaches the osteoblasts of interest, such that the desired effect is produced.. It is recommended that the claims be amended such that separate claims are written on the *in vitro* assay method, and the *in vivo* assay method.

Claims 7 and 8 are indefinite because the claims read on both an *in vitro* assay and an *in vivo* assay method, but it is unclear as to how the methods of the independent claim 6 could be used in an *in vitro* animal model. As a second issue, the specification seems to teach that *ex vivo*

hisomorphometry methods were used to determine the bone changes in the animal model. Therefore, Applicant's claim to an *in vivo* assay method are unclear and indefinite, since *ex vivo* methods are used. In the absence of clarity, the metes and bounds of the claimed invention cannot be determined.

Claims 12 and 13 are indefinite because the claims read on both an *in vitro* assay and an *in vivo* assay method, but it is unclear as to how the methods of the independent claim 11 could be used in an *in vitro* animal model. As a second issue, the specification seems to teach that *ex vivo* hisomorphometry methods were used to determine the bone changes in the animal model. Therefore, Applicant's claim to an *in vivo* assay method are unclear and indefinite, since *ex vivo* methods are used. In the absence of clarity, the metes and bounds of the claimed invention cannot be determined

Claim 9 recites the limitation "said murine animal model". There is insufficient antecedent basis for this limitation in the claim. No reference to a murine animal model is made in the independent claim 6. In the absence of clarity, the metes and bounds of the claimed invention cannot be determined.

Claims 10 and 14 are indefinite in their recitation of "said determination of apoptotic cells is selected from the group consisting of microscopy of stained cells, TUNEL, Hoescht 33258 dye, and video image analysis." The phrase is vague and indefinite, because microscopy of stained cells, TUNEL, Hoescht 33258 dye, and video image analysis are not species of "determination". In the absence of clarity, the metes and bounds of the claimed invention cannot be determined. It

is recommended that "said determination step is selected from the group consisting of microscopy of stained cells, TUNEL, Hoescht 33258 dye, and video image analysis."

Claims 11-14 are indefinite in their recitation of "said osteoblast cells" in line 9 of claim 11, and in line 2 of claim 12. It is unclear whether these osteoblast cells are the pre-glucocorticoid treated osteoblast cells, or the glucocorticoid treated osteoblast cells. In the absence of clarity, the metes and bounds of the claimed invention cannot be determined. It is recommended that the specific osteoblast cells be incorporated into the claim language.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 6, 9 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Hill et al. (1997).

Claim 6 is drawn to a method of screening for a compound that stimulates bone formation, comprising the steps of contacting osteoblast cells with a test compound, determining the number of cells undergoing apoptosis, and comparing the number of apoptotic cells with osteoblast cells that have not been contacted with said compound, wherein fewer apoptotic cells following contact with said compound than in the absence of said contact indicates that said compound

inhibits apoptosis resulting in stimulation of bone formation. Hill et al. teach an in vitro assay where calvarial osteoblasts were contacted with multiple growth factors, cytokines, and osteotrophic hormones. The rate of osteoblast apoptosis in the test cultures was compared to the rate of control osteoblast apoptosis. Test compounds that resulted in a reduced rate of apoptosis as compared with the control was indicative of a compound that inhibits apoptosis, thereby resulting in bone formation. See entire article. The bone formation measurement methods of claim 9 and 10 in the instant application were well known and widely used at the time the invention was made. See for example, Hilliker et al. (1994), Jilka et al. (1996), Lecka-Czernick et al. (1997), Okamoto et al. (1995), Gunness et al (1993), Cornish et al. (1995), Meng et al. (1996), and Hill et al. (1997). Therefore, the in vitro assay of Hill et al., and the bone formation measurement methods known in the art meet the limitations of the claimed invention.

Prior Art

At the time the invention was made, the following was known in the art:

The SAMP6 mouse was known as a murine model of age related spontaneous osteopenia, characterized by low peak bone mass. (Okamoto et al. 1995, Abstract; Lecka-Czernik et al. 1997, entire article; Jilka et al. 1996, entire article). The SAMR1 mouse was known as a murine model of accelerated senescence resistance. (Fujibayashi et al. 1994, Abstract). The administration of parathyroid hormone and its analogs by various systemic routes (including oral, intravenous, intra-nasal, and inhalation) to human patients for the purpose of promoting bone

formation in said human patients was also known. (Chorev et al. 1998, Abstract; Hilliker et al. 1994). It was also known in the art that glucocorticoid administration could induce osteopenia in mammals (Vickery, 1998). The art also taught that bPTH and hPTH increases whole body calcium and ash weight of individual bones in both normal and osteoporotic adult female rats; and that daily subcutaneous injections of hPTH(1-34) completely reverses the loss of trabecular bone and results in amounts of trabecular bone exceeding that of controls, as well as an increase in the number of osteoblasts, and a decrease in the number of osteoclasts; and that daily subcutaneous injections of hPTH(1-34) to healthy adult male rats increased total bone mass, trabecular bone volume, trabecular thickness and number, and osteoblastic surfaces. (Vickery, 1988, column 2, lines 29-49; Cornish et al., entire article). It was also known in the art that an increase in PTH-induced bone growth is due to an increase in adenylyl cyclase activity. (Morley et al. 1999, column 2, lines 40-43). The art also taught that PTH stimulates the rate of bone resorption by osteoclasts, increases the rate of differentiation of mesenchymal cells to osteoclasts, prolongs the half life of osteoclasts, increases the number of bone forming osteoblasts, but decreases the activity of individual osteoblasts. (Piazza et al. 1999, column 3, lines 37-42). Gunness et al. (1993) taught that PTH treated rats exhibit an increase in the number of osteoblasts, and an increase in the surface extent of osteoid and osteoblasts. The authors also taught that the anabolic effect of PTH on bone can be primarily attributed to activation and stimulation of osteoblast function. See page 278, paragraph 2, and page 279, last paragraph. Finally, the prior art of record teaches that osteoblast apoptosis is reduced, and osteoblast survival is increased, by

insulin-like growth factor I, insulin-like growth factor II, insulin, and basic fibroblast growth factor. However, the prior art of record does not teach a method of reducing the number of osteoblasts undergoing apoptosis in an osteopenic patient comprising administering hPTH(1-34) to said patient. Therefore, claims 1-5, 7, 8, and 11-14 are free of the prior art of record.

Conclusion

No claim is allowed, for the reasons outlined above.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kris Pelham Mayo whose telephone number is (703) 306-5877. The examiner can normally be reached on Monday-Friday from 8:00 a.m. to 4:30 p.m. (Eastern Time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached at (703)308-2035. The FAX phone number for group 1600 is (703)308-4242.

An inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is (703)308-0196.

Kris Pelham Mayo, D.V.M.
Patent Examiner
Art Unit 1633
December 20, 1999

Karen M. Hauda
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